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EXAMINER

HM32/0608

ART UNIT	PAPER NUMBER
1641	7

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DATE MAILED: 06/08/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 3/18/98

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 2-5 and 7-8 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 2-5 and 7-8 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
*Certified copies not received: _____
☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

CHANGE IN ART UNIT

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit **1641**.

PAPER ENTRY

The petition under 37 CFR 1.136 filed March 18, 1998 (paper no. 5) for a two month extension of time is acknowledged and has been granted.

The **AMENDMENT** filed March 18, 1998 (paper no. 6) is acknowledged and has been entered.

CLAIM STATUS

Claims 1 and 6 have been cancelled. Claims 2 and 5 have been amended. New claims 7 and 8 have been added. Claims 2-5 and 7-8 are pending.

DRAWINGS

The drawings are objected to for reasons of record (see PTO-948 attached to paper no. 4) Corection is required.

The Figure and all references to the Figure in the specification should be amended to refer to --Figure 1--. See paper no. 4, pages 2-3 for Information on How to Effect Drawing Changes.

Applicant argues identification of the sole figure of the application as Fig. 1, implies that there would be additional figures. Thus, identification of the sole figure as Fig. 1 would be incorrect.

In response, 37 CFR 1.84(t) requires the numbering of sheets of drawings. Secondly, since the face of a patent explicitly notes the number of drawing sheets, designation as Fig. 1 would not be unduly confusing.

ABSTRACT

The abstract of the disclosure is objected to because it does not mention the claimed analytical system. Correction is required. See MPEP § 608.01(b).

PRIOR CITATION OF TITLE 35 SECTIONS

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

NON-ART BASED REJECTIONS

Claims 2-5 and 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Use of inconsistent terminology is confusing. Please clarify the difference between "comprising" and "containing". If there is no difference, a single term should be used. If there is a difference, that difference should be clarified.

Claim 7 lacks antecedent basis for "the detection" (line 1, e.g. by conventional Raman spectroscopy, by resonance enhanced Raman spectroscopy, etc.); "the range" (line 5); "the nucleic acids" (line 8); and "the Raman fingerprint region" (line 10). The metes and bounds of "the Raman fingerprint region" are indeterminate. Claim 7 is confusing in reciting antibodies

"attached to a surface" (line 2) and "sensing" (line 7). It is unclear whether a biosensor is intended (which would require a transducer and a sensing surface); or, whether there is no structural limitation being implied (e.g. a reaction vessel or cuvette comprising (a) antibodies immobilized on surfaces of latex microspheres and (b) an aqueous sample suspected of containing the specific microorganism, wherein the vessel/cuvette is irradiated and the Raman emissions are recorded). Claim 7 implies, rather than positively states, a sample to be tested for the specific microorganism has been contacted to the immobilized antibodies. Claim 7 is vague and indefinite as to the relationship between the antibody(ies), the microorganism(s), the antigen and the complex as well as the relationship between the incident light energy, the Raman spectroscopy and the "fingerprint region". Claim 7 is vague and indefinite in reciting "proportionally very much larger numbers" and "substantially in the absence" as the metes and bounds of the number of antibodies and incomplete lack of fluorescence are indeterminate. Claim 7 is incomplete in failing to recite a method step of detecting the specific microorganism as proscribed in its preamble. Claim 7 is confusing in reciting "fluorescence" because it is unclear what the "fluorescence" has to do with the excited nucleic acids and/or the detecting step and/or the selection of the laser light and/or that such fluorescence impliedly would originate from the immobilized antibodies. The following language, or its equivalent, is suggested as a beginning template for applicant's consideration, NOT as a proposed allowable claim.

> A method for detecting the presence of a specific microorganism in a sample, said microorganism having a characteristic resonance enhanced Raman

backscattered energy spectrum produced by irradiating nucleic acids in said microorganism at a wavelength between 242-257 nm, comprising:

(a) contacting said sample with a medium comprising solid phase immobilized antibodies which specifically bind to a characteristic cell surface antigen on said microorganism to form an antigen-antibody complex, thereby immobilizing said microorganism on said solid phase;

(b) irradiating the solid phase of step (a) with a laser light of 242-257 nm to produce a resonance enhanced Raman backscattered energy spectrum; and,

(c) comparing said induced spectrum of step (b) with said characteristic spectrum to detect the presence of said microorganism in said sample.

Claim 3 lacks antecedent basis for "the light energy". Secondly, it is unclear how claim 3 (and claim 4) further limits new claim 7 because 242-257 laser light is, by definition, ultraviolet light, as emphasized by claim 4 which redundantly recites the ultraviolet light to be in the rangeof 242 to 257 nm.

It is suggested that claim 5 be written as --The method of claim 7 wherein the solid phase of step (a) is washed to remove unbound sample and medium before irradiating step (b).--, or equivalent.

Analogous criticisms and comments apply to claim 8. In addition, it is unclear whether claim 8 intends the system to include a medium with antibodies attached to a surface because no surface with immobilized antibodies is positively recited in the body of claim 8. As presently written claim 8 only requires the instantly recited (1) irradiating, (2) sensing and (3) detecting means.

Claims 2-5 and 7-8 fail to set forth the subject matter which applicant(s) regard as their invention for reasons of record (see paper no. 4, pages 6-7). In particular, the claims do not recite detection of a peak at 1485 cm^{-1} and/or explain the relationship of this peak with the now recited "Raman fingerprint region"; or, production of resonance enhanced Raman spectrum of backscattered lower energy.

Claims 3 and 4 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. See the discussion *supra*.

Claims 2-5 and 7-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to provide a fully enabling disclosure for reasons of record (see paper no. 4, pages 7-8). In particular, the claimed invention is only enabled for resonance enhanced Raman spectroscopic analysis and systems.

ART BASED REJECTIONS

Please note that claim 8 is interpreted as only requiring the recited (1) irradiating, (2) sensing and (3) detecting means. The intended functional use with surface comprising immobilized antibodies recited in the preamble has not been read as a positive structural limitation. According to the specification, such a system comprises (1) a laser light, (2) a Raman detector and (3) a display. The claimed invention is interpreted in light of this disclosure and *In re Donaldson Co.*, 16 F.3d 1189, 29 USPQ2d 1845 (Fed. Cir. 1994).

Claims 2-5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chadha et al. (*Review of Scientific Instruments*, 64(11):3088-3093, **1993**) in view of Nelson et al.

(*Applied Spectroscopy Reviews*, 27(1):67-124, **1992**) and either Szoka (US 4,483,929) or Newman (US 4,822,566).

Claim 8 is rejected under 35 U.S.C. 102(b) as being anticipated by Chadha et al.(*Review of Scientific Instruments*, 64(11):3088-3093, **1993**).

Chadha et al. describe a method and an ultraviolet micro-Raman spectrograph therefore for detecting bacterial cells as claimed with the exception of immobilizing the bacterial cells via polylysine instead of the instantly recited antibody. Chadha et al. note on page 3091 (col. 2, ¶2)

> Bacterial cells can be motile and move away from the laser beam. To immobilize bacteria very small dilute bacterial suspensions were placed on quartz plates coated with 0.01% polylysine and pressed down with a quartz cover slip. Bacterial cells treated in this fashion were fixed on the plates by the polylysine which acted as an adhesive.

Nelson et al. state on page 79, ¶3 that "the DNA and cell surface antigens are in principle the *most attractive targets as potential markers for bacterial identification*" (emphasis added).

Both Szoka (see e.g. ¶ bridging cols. 10-11) and Newman (see e.g. Table 1 in col. 6) describe the conventional use of biospecific antibodies to immobilize bacterial or viral analytes for assay.

It would have been obvious to one of ordinary skill in the art to modify the method and system of Chadha et al. by substituting biospecific antibody for the disclosed polylysine not only because biospecific antibodies are conventionally used to immobilize bacterial and viral analytes for assay, but also because combining the DNA analysis of Chadha et al. with the selectivity/specificity of an antigen-antibody immobilization would combine the two most

attractive markers for bacterial identification, as suggested by Nelson et al., thereby resulting in a more efficient identification/detection system and method. No unexpected results are seen. The claimed detection "in the presence of an excess of antibody" is inherent in the UV resonance enhanced Raman method/spectrograph of Chadha et al.

Traversal/Rebuttal

I. Applicant argues one would not have expected the above combination to work, i.e.

> what is most expected is an interference from the aromatic components of the antibody. If the resonance Raman method is to be effective in sensitive detection, neither fluorescence interference nor the background resonance Raman interference of the antibody can be present. Both must be essentially absent or significantly suppressed to allow the sensitive detection of the nucleic acid peaks, and specifically the 1485 cm^{-1} peak.
>
> The behavior of the antibody fluorescence is predictable. Fluorescence intereference is known not to be problem with 242 and 521 nm excitation especially. **But the very low intensity and degree of interference of the resonance Raman spectra of the antibody is an unexpected surprise**. (emphasis added, paper no. 6, page 5, ¶¶2,3)

especially given the very large excess of antibody used to increase the probability of bacterial capture.

II. Applicant profers that Chadha et al. used polylysine specifically because it contains no aromatic amino acids which are expected to interfere with the resonance Raman spectra of bacteria.

III. While Newman takes advantage of the selective formation of antigen-antibody complexes and Szoka uses FIA, RIA and ELISA labeling methods, they are different from the disclosed

method of detection, the items detected and several orders of magnitude less sensitive than the claimed method.

* In response, arguments drawn to **resonance** Raman methods, excitation at 242 nm or detection of the 1485 cm^{-1} peak are not commensurate in scope with the claimed invention; and, therefore, are not convincing of patentability.

I. According to Chadha et al.

> ...resonance Raman spectra of ... bacteria and bacterial spores, excited at 200-257 nm have been reported. ... Taxonomic markers most strongly excited tend to be protein aromatic amino acids, nucleic acids and dipicolinic acid. ... Availability of UV lines between 200 and 257 mn, and the fact that the absorption wavelength maxima of the markers vary, allows selective enhancement of a number of vibrational modes associated with UV absorbing chromophores. With 242, 252, and 257 nm excitation, vibrational modes of various nucleosides, nucleic acids, quinones, and calcium dipicolinate are selectively excited. Excited at 231 and 222 nm, all spectra reflect almost exclusively protein aromatic acids and proline bands. (page 3089, col. 1, ¶2)

Thus, Chadha et al. suggests that one of ordinary skill in the art would selective an excitation wavelength appropriate to the taxonomic marker(s) of interest. Using nucleic acids as the taxonomic marker, one would have been motivated to use 242, 252 or 257 nm excitation. Indeed, Chadha et al. explicitly suggests that excitation near 242 nm promises better signal to noise because of reduced background fluorescence (page 3092, col. 2, last ¶). The merits of such selective excitation are mirrored by Nelson et al.

> ...resonance Raman...allows the study of very small amounts of the biologically-active species in the presence of large amounts of potentially interfering substances. Its potential millionfold increase in sensitivity coupled with the capability to selectively excite modes associated with a chromophore of interest

> makes resonance Ramn a powerful tool which can be useful in attacking problems of biological interest. (page 73, ¶3)

See also page 78, ¶¶ 1,2. More specifically, Nelson et al. state

> The first UV resonance Raman studies of whole bacterial cells were accomplished at **242 nm excitation** [67]. **It was expected that since this wavelength corresponds very nearly to the protein absorption minimum, spectra would contain nucleic acid modes primarily. Indeed, at 242 nm, nucleic acid symmetric vibrations were strongly excited along with *very few* tryptophan and tyrosine modes**. (emphasis added, page 84, ¶4)

Therefore, it is respectfully submitted that the Chadha et al. and Nelson et al. both provide clear suggestions as to how to maximize nucleic acid based spectra and minimize protein based spectra in near UV resonance Raman systems, e.g. by using 242 nm excitation.

Arguments drawn to relative amounts of antibody protein versus microorganism/microbial protein are inconclusive. Neither the claimed invention nor the references provide data as to the amount of total protein in the analyzed sample. However, the data suggests that 50 ng of bacterial protein and 50 ng of antibody protein under identical environmental/experimental conditions should both show very few tryptophan and tyrosine modes at 242 nm excitation because this wavelength corresponds very nearly to the protein absorption minimum.

Therefore, these arguments are not persuasive.

II. Chadha et al. is silent as to the reason polylysine was **specifically used**. In the alternative, applicant is respectfully requested to point out by page and line number where the proferred reason can be found in Chadha et al. Assuming *arguendo* polylysine was used because it did not contain aromatic amino acids, it is respectfully submitted that both Chadha et al. and Nelson et al.

suggest use of 242 nm excitation to minimized aromatic amino acid, i.e. protein, interference as stated *supra*.

Therefore, this argument is not persuasive.

III. It is agreed that Newman and Szoka rise or fall with Chadha et al. and Nelson et al. They have been applied simply to show the conventionality of antibodies as capture reagents for microorganisms.

The rejections of claim 8 under 35 U.S.C. 102(b) as being clearly anticipated by Malmqvist et al. (US 5,492,840) or Bogart et al. (US 5,468,606); or, under 35 U.S.C. 102(a)/(e) as being clearly anticipated by Herron et al. (US 5,512,492) are moot in view of the cancellation of claim 8.

CLOSING

In conclusion, applicant's amendments and arguments filed March 18, 1998 have been fully considered but are not deemed convincing of patentability for the above reasons and reasons of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant's request for a telephone interview on page 8 of paper no. 6 is noted. A voice mail message was left for Mr. Richard L. Stevens the morning of June 2 stating the examiner was currently working on this application and would be available through close of business June 3, 1998 for his input. No return telephone call has been received as of 6 pm on June 3, 1998.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carol A. Spiegel whose telephone number is (703) 308-3986.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Carol A. Spiegel

CAROL A. SPIEGEL
PRIMARY EXAMINER
GROUP ~~1600~~ 1600

Carol A. Spiegel
June 3, 1998